Genetic Evidence on Modern Human Origins

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Abstract A review of genetic evidence leads to the following conclusions concerning human population history: (1) Between 33,000 and 150,000 years ago the human population expanded from an initial size of perhaps 10,000 breeding individuals, reaching a size of at least 300,000. (2) Although the initial population was small, it contained at least 1000 breeding individuals. (3) The human races separated several tens of thousands of years before their separate expansions. (4) Before their expansions the separate racial populations were small. These inferences are inconsistent with both the multiregional and the replacement models of modern human origins. They support the "weak Garden of Eden" hypothesis, which holds that the human populations separated some 100,000 years ago but did not expand until tens of thousands of years later.

In recent years genetic evidence has played an increasing role in discussions about the origin of modern humans. More often than not, the discussion has been heated. Opinions about the value of genetic evidence range across all possible extremes. Even those who think the evidence is of value disagree about what it implies.

The debate has focused on two competing hypotheses (Stringer and Andrews 1988). According to the *multiregional hypothesis*, the major subdivisions of our species evolved in situ over a long period of time, with gene flow accounting for much of the similarity now observed among groups (Wolpoff 1989; Frayer et al. 1993). In contrast, the *replacement hypothesis* holds that earlier populations were replaced 30,000–100,000 years ago by populations of anatomically modern humans that originated in Africa (Stringer and Andrews 1988).

Recently, new models and statistical methods have provided new ways to use genetic data in testing hypotheses and estimating parameters related to demographic history (Rogers and Harpending 1992; Harpending et al. 1993; Rogers 1994a,b). These estimates led Harpending et al. (1993) to introduce a third hypothesis of modern human origins. Their *weak Garden of Eden hypothesis* holds that a small ancestral human pop-

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ulation separated into several partially isolated groups approximately 100,000 years ago. Then, about 30,000 years later, these groups underwent either simultaneous bottlenecks or simultaneous expansions in size. The new window into demographic history also provides new insights into the meaning of other forms of genetic data. Here, we review these new findings and use them to reassess the genetic evidence on modern human origins.

For several years now the genetic literature on modern human origins has relied heavily on genealogical trees inferred from mitochondrial DNA (mtDNA). We begin our review with a discussion of what is wrong with this approach.

Problem with Mitochondrial Trees

Several trees inferred from worldwide samples of human mtDNA have their deepest branches within the African population (Cann et al. 1987; Vigilant et al. 1991), and this fact has been interpreted as support for an African origin of the modern human population. However, recent research has challenged the estimated trees that underlie this inference (Maddison et al. 1992; Templeton 1992; Hedges et al. 1992; Templeton 1993; Gibbons 1992). It now appears that the observed pattern was an artifact resulting from the order in which observations were entered into the computer program.

Subsequent research has shown that the human mtDNA tree is extraordinarily difficult to estimate. Many thousands (perhaps millions) of trees are consistent with the data, and it seems impossible to choose among them. Although this low phylogenetic resolution is unfortunate for those who wish to build trees, it also provides information: It suggests that the human population has undergone a relatively recent expansion in size. To see why, consider the upper two panels of Figure 1. The upper panel shows the history of a hypothetical population, and the middle panel shows the genealogy of a sample of 50 individuals drawn from this population. This is the true genealogy of our hypothetical sample, not an estimate. In both these panels, the horizontal axis measures time backward from the present on a "mutational" time scale in which each unit is equal to $1/(2u)$ generations, where u is the mutation rate. For purposes of discussion we assume that $u = 0.0015$.[1] With generations of 25 years, this makes each unit of mutational time equal to 8333 years.

The hypothetical population experienced a 500-fold expansion at 7 units of mutational time (or 58,000 years) before the present.[2] This expansion has a profound effect on the genealogy. The vertical lines in the genealogy mark points at which two lineages have a common ancestor and coalesce into a single lineage. Coalescent events are rare in the pe-

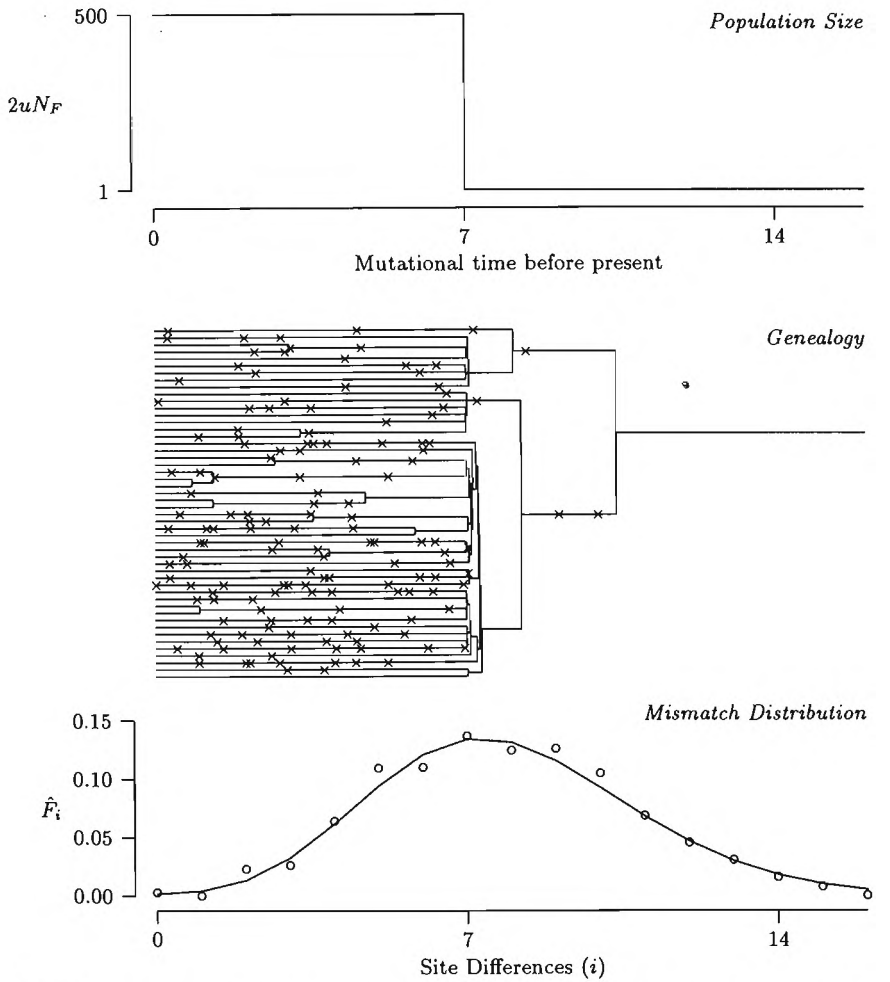

Figure 1. Mitochondrial genealogy and mismatch distribution of a hypothetical population. The top panel shows $2uN_F$ as a function of time before present, with time measured in units of $1/(2u)$ generations. The population was small before time 7. The middle panel shows the genealogy of a sample of 50 individuals drawn from this population, which was generated by an algorithm that assumes selective neutrality (Rogers 1994b). The crosses represent mutations. The open circles in the bottom panel show these same data as a mismatch distribution; the solid line shows the theoretical mismatch distribution for the parameters of the hypothetical population.

riod from the expansion to the present; most of them occur in a brief interval just before the expansion. This is no accident. In a large population a random pair of individuals is unlikely to have the same mother. Consequently, coalescent events occur only rarely in the large post-expansion population. But before the expansion the population was small, a random pair was much more likely to share the same mother, and coalescent events therefore occurred rapidly. As a result, coalescence events are concentrated in a narrow interval of time. This pattern occurs not only in the simulated genealogy in Figure 1 but also in genealogies estimated from human mtDNA [see, for example, Di Rienzo and Wilson (1991)]. Indeed, we have never seen a worldwide human mtDNA genealogy that lacks this pattern.

The crosses on the genealogy in Figure 1 represent mutations, which occur randomly along each branch. In this hypothetical population 37 of the 49 coalescent events occurred before the expansion, yet 143 of the 150 mutations occurred after. Consequently, only 7 mutations are available for dating the 37 clades that antedate the expansion. Clearly, no statistical method could tell us much about the relative ages of these 37 clades; the data are essentially devoid of phylogenetic information.

Thus the low phylogenetic resolution of human mtDNA would make sense if the human population had undergone an expansion. This hypothesis is strengthened by the observation that estimates of the human mtDNA tree often exhibit the pattern seen in Figure 1, in which many coalescent events are compressed into a brief interval of time (Di Rienzo and Wilson 1991). Hasegawa et al. (1993) infer from this pattern that an expansion of the human population occurred at 89,000 ± 69,000 years ago. We offer additional evidence to this effect later.

It is interesting that the very pattern that obscures phylogenetic information also provides information about population history. This suggests an uncertainty principle: It may be impossible for data to inform us simultaneously about gene genealogy and about the history of population size.

Waves in the Mismatch Distribution

Recent estimates of human demographic history have been based on the mtDNA mismatch distribution (or the distribution of pairwise genetic differences), an example of which is shown by the open circles in Figure 2. The mismatch distribution is obtained by counting the number of nucleotide (or restriction) site differences between each pair of individuals and assembling the resulting counts into a frequency histogram or scatter plot. Human mismatch distributions are usually smooth and wave shaped, as shown in Figure 2. Rogers and Harpending (1992) argue

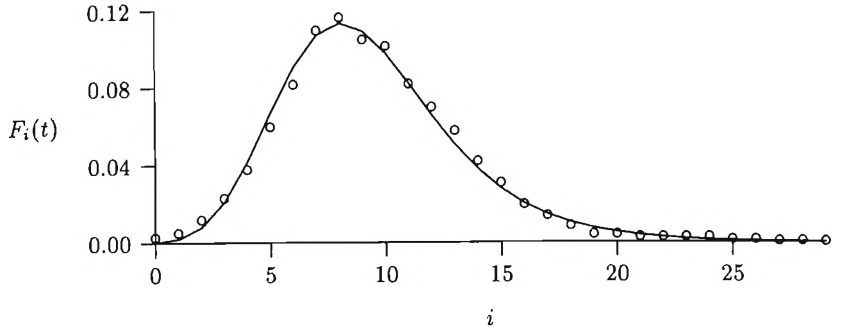

Figure 2. The model of sudden expansion fit to the data of Cann et al. (1987). The open circles show the relative frequencies of pairs of individuals whose mtDNA samples differ by i sites in the data of Cann et al. (1987, Figure 1). The solid line shows the fit of the nonequilibrium distribution (Rogers and Harpending 1992) obtained using the two-parameter method of moments estimator (Rogers 1994a).

that this pattern is the signature of an ancient population expansion. The shape and position of the wave provide information about the timing and the magnitude of the expansion (Harpending et al. 1993; Rogers 1994a).

To make these claims credible, we first explain why population expansions generate waves in the mismatch distribution. To this end, we use the simulated sample in the middle panel of Figure 1 to calculate a mismatch distribution. If we assume that each mutation separating a pair of individuals produces a detectable nucleotide site difference [the so-called model of infinite sites (Kimura 1971)], then the number of site differences between a pair of individuals is obtained by counting the crosses along the path connecting them. For example, there are four site differences between the topmost pair of individuals in the genealogy (see Figure 1). With 30 individuals in the sample there are 435 pairs of individuals, and we calculate the number of differences between each pair. Assembling these 435 differences into a histogram or scatter plot produces the mismatch distribution shown in the lower panel of Figure 1. Notice that the distribution peaks just to the right of the point $i = 7$. This is because many pairs of individuals are separated by just over 7 units of mutational time. Thus the wave in the mismatch distribution peaks at a point just before the population expansion and corresponds to the part of the genealogy at which coalescent events are concentrated.

The word *wave* is appropriate here not only because the mismatch distribution is shaped like one but also because it moves like one. As time goes by, mutations accumulate along the branches connecting each pair of individuals. This pushes the wave to the right at a constant rate, traversing each unit of the horizontal axis in $1/(2u)$ generations (Rogers and Harpending 1992). Thus the mutational time scale makes the hori-

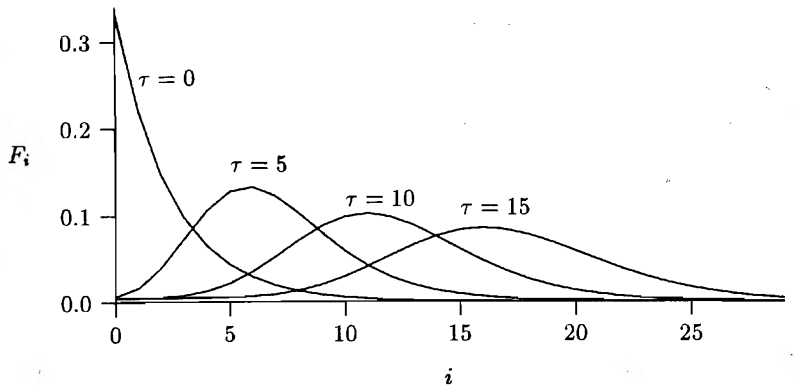

Figure 3. How a population expansion affects the theoretical mismatch distribution. Theoretical mismatch distributions for various values of τ, assuming that θ increased in value from $\theta_0 = 2$ to $\theta_1 = 200$ at τ units of mutational time before the present.

zontal axes of the upper two panels of Figure 1 correspond to the horizontal axis of the mismatch distribution.

The mismatch distribution is often analyzed using models that assume an equilibrium between mutation and genetic drift (Tajima 1983; Avise et al. 1988). However, mismatch distributions from simulated equilibrium populations are ragged, with multiple peaks, and look nothing like the smooth curve in Figure 2. Indeed, the equilibrium hypothesis can be rejected on the basis of the observed distribution's smoothness alone (Harpending 1994). To reach stronger conclusions, we must model the effect of population growth on the mismatch distribution.

For nonrecombining genetic systems, such as mitochondria, simple formulas allow us to calculate what we call the theoretical mismatch distribution from any assumed trajectory of population size (Li 1977; Rogers and Harpending 1992). We confront a problem, however, in applying this theory to real data. The theoretical mismatch distribution pertains to differences between a *single pair* of individuals. Yet we wish to apply this theory not to single pairs but to empirical distributions that were calculated using many pairs. Simulations show that in equilibrium populations the empirical curves look nothing like the theoretical ones. Fortunately, the fit is much better in populations that have expanded within the past 100,000 years or so. This does not justify using the theory as a basis for statistical inference, but it does make the theory useful as a guide to intuition.

Figure 3 shows the effect of a population expansion on the theoretical mismatch distribution. The population expansion generates a wave that moves from left to right at a constant rate $1/(2u)$ per generation. If,

as we assumed earlier, each unit of the horizontal axis corresponds to 8333 years, then the advance of the wave in Figure 3 from mutational time 0 to mutational time 15 would take about 125,000 years. Because of this slow rate of change, the mismatch distribution is useful for studying events that happened well back into the Pleistocene.

To characterize any population trajectory completely would require estimating a parameter (the population size) for each point in time. We must settle for less than this because it is never possible to estimate more than a few parameters at once. Therefore our statistical analysis has used a simplified representation of population history that we call the model of sudden expansion (Rogers and Harpending 1992). The name is somewhat misleading, since the model can accommodate zero growth and negative growth as well as the positive growth that its name implies. The model assumes that population growth (if any) was restricted to a brief episode t generations ago. Before this episode the population was at equilibrium between mutation and genetic drift. Afterward, the population remained constant in size. Although this model is unrealistically simple, it is robust enough to be useful even in populations with complex demographic histories (Rogers and Harpending 1992).

The model involves three parameters:

$$\theta_0 \equiv 2N_0u, \tag{1}$$

$$\theta_1 \equiv 2N_1u, \tag{2}$$

$$\tau \equiv 2ut, \tag{3}$$

where u is the total mutation rate over all sites in the sample, N_0 is the female population size before expansion, N_1 is the size after expansion, and t is the time in generations since the expansion. Rogers (1994a) has developed statistical methods that estimate these parameters. His estimates were used to fit the curve in Figure 2, which provides an excellent description of the data. However, this close fit is no reason for confidence in the method. Instead, the method is justified by simulations, which show that the estimators are well behaved, with modest standard errors (Rogers 1994a). The estimates indicate that the human population expanded dramatically some $7/(2u)$ generations ago—about 60,000 years ago. Similar conclusions have been obtained from many other human data sets (Sherry et al. 1993).

To generate a confidence interval, Rogers (1994a) simulated 1000 data sets at each of a wide variety of parameter values. At each parameter value he used the simulated data to test the hypothesis that those parameters could have generated data "at least as extreme" as the data shown in Figure 2 [this test is described in full elsewhere (Rogers 1994a)]. The set of parameter values that could not be rejected at the 0.05 significance level constitutes a 95% confidence region and is shown in Figure 4.

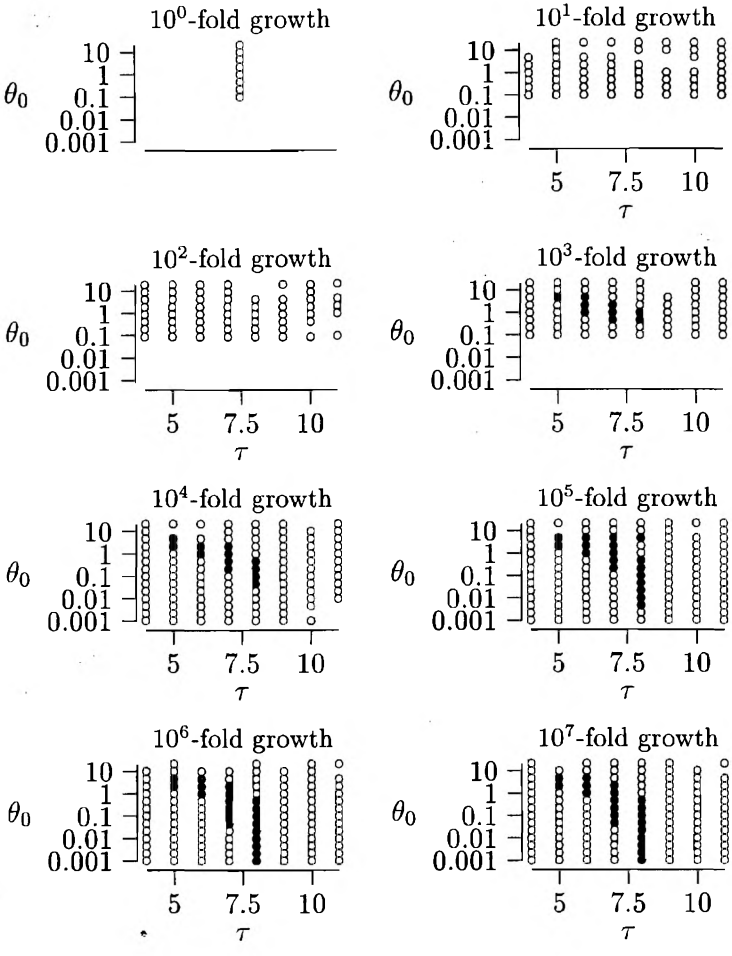

Figure 4. A 95% confidence region for the Cann et al. (1987) data. Filled circles indicate points within the 95% confidence region, and open circles indicate points outside the confidence region. 10^v-fold growth means that $\theta_1/\theta_0 = 10^v$. This is an expanded version of Rogers's (1994a, Figure 8) confidence region.

The open circles in the confidence region indicate parameter values that were rejected and are therefore outside the confidence region. The filled circles indicate points within the confidence region. Because the confidence region excludes all parameter values that imply that growth was 100-fold or less, the evidence for population expansion is clear. An expansion of this magnitude—even one that happened quickly—is not implausible. The world human population is now growing at about 1.5% per year, and the Yanomamo (an expanding horticultural population) are

growing at about 2% per year. Thus a 1% rate of increase is well within human capabilities, and at this rate a 1000-fold increase would require 700 years.

τ measures the time since the expansion in units of $1/(2u)$ generations. The confidence region implies that $4 < \tau < 9$ with 95% confidence. If the nucleotide divergence rate is 4% per million years (Cann et al. 1987), then $u = 1.5 \times 10^{-3}$ (Rogers and Harpending 1992). With generations of 25 years the confidence interval for τ then corresponds to 33,000–75,000 years B.P. If the nucleotide divergence rate is really 2% per million years (Cann et al. 1987), then $u = 7.5 \times 10^{-4}$ and the interval for τ becomes 66,000–150,000 years B.P. Neither of these ranges is a proper confidence interval because neither takes proper account of the sampling variation in our estimated divergence rates. Nonetheless, if the true value of u is somewhere in the neighborhood of these estimates, then the population expansion must have occurred during the late Pleistocene.[3]

The confidence interval also implies that $\theta_0 < 10$. With the smaller estimate of u this gives approximately $N_0 < 7000$, which is in good agreement with earlier estimates of population size (Haigh and Maynard Smith 1972; Brown 1980; Jones and Rouhani 1986; Maynard Smith 1990; Wills 1990; Rogers and Harpending 1992). Thus it appears that sometime in the late Pleistocene the ancestral human population contained no more than a few thousand breeding females.

How large was the postexpansion population? In the panel for 10^3-fold growth (Figure 4), 0.46416 is the smallest value of θ_0 within the confidence region, so this panel implies that θ_1 may be as small as $10^3 \times 0.46416 = 464$. Repeating this exercise in the panels for 10^4- and 10^5-fold growth (the only panels in Figure 4 that define a lower bound for θ_0) gives the same answer. Thus 464 is apparently the lower edge of the confidence region for θ_1. Dividing by twice the mutation rate (and using the larger estimate of u), we find that the postexpansion population must have included at least 150,000 breeding females, or 300,000 breeding individuals.

This confidence region assumes (unrealistically) that the entire human species mates at random. Nonetheless, it has been largely vindicated by subsequent research using a geographically structured model (Rogers 1994b). The structured model requires two revisions of the random-mating confidence region. First, if the postexpansion population is structured, then the expansion need not be quite as large—100-fold is enough. Second, if the pre-expansion population is structured, then the initial population must be even smaller. With strong migration (between 1 and 100 migrants per generation between each pair of groups) the confidence region requires that $\theta_0 < 2.15$, a value only one-fifth as large as the upper bound under random mating. With weak migration the upper bound is

even smaller. This implies that if the initial population was structured, then it cannot have included more than 1500 breeding females.

Waves in the Intermatch Distribution

In a subdivided population we can calculate mismatch distributions using pairs drawn either from a single subdivision or from different subdivisions. Following Harpending et al. (1993), we refer to the latter as intermatch distributions. In presenting ideas about intermatch distributions, we ignore gene flow in order to simplify the exposition. Gene flow is then introduced in the simulations used to evaluate these ideas.

A wave in an intermatch distribution may reflect either of two types of events. First, it may reflect an expansion that occurred before the separation of an ancestral population. When a population expands and later splits into several subdivisions, the wave produced by the earlier expansion will continue to dominate the mismatch distribution within each subdivision and the intermatch distribution between each pair of subdivisions. Thus the intermatch and mismatch distributions are nearly identical.

The result is different, however, when there is no wave in the original distribution. Then, separation of a population produces a wave in the intermatch distribution that does not appear in the mismatch distributions. Like the mismatch waves in Figure 3, this intermatch wave will move from left to right at a constant rate of $1/(2u)$ per generation. In fact, the intermatch distribution evolves just like the mismatch distribution of an infinite population. This makes it possible to study intermatch waves using the same methods that are used for the mismatch waves.

Figure 5 compares the mismatch and intermatch distributions of three pairs of populations. The left-hand panel compares the Asian and Middle Eastern populations, for which the two mismatch distributions are nearly identical both to each other and to the intermatch distribution. As discussed, this pattern suggests that an expansion either preceded or coincided with the separation of these populations. The latter possibility is consistent with the replacement hypothesis of modern human origins.

In the center panel of Figure 5 the distributions of the !Kung and Nuu Chah Nulth show a different pattern. There, the intermatch distribution leads the two mismatch distributions by an interval that Harpending et al. (1993) estimate at close to 50,000 years. This pattern occurs frequently in pairs of human populations; the mean excess of intermatch waves over mismatch waves amounts to about 30,000 years (Harpending et al. 1993). How could this pattern have arisen? Harpending et al. (1993) show that such patterns are unlikely to arise when a

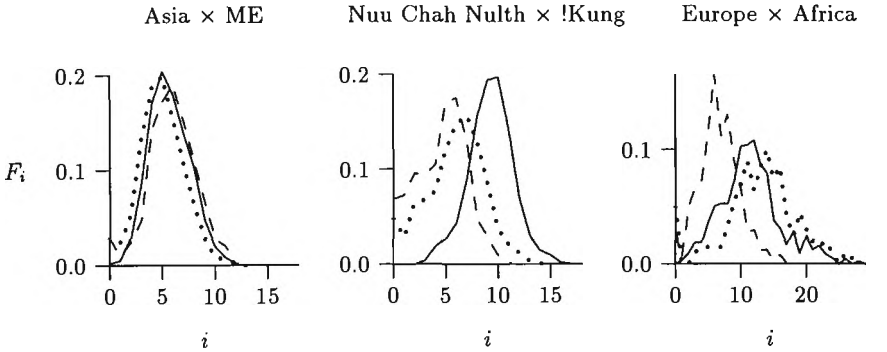

Figure 5. Mismatch and intermatch distributions. Dashed lines are used for mismatch distributions of Asia, Nuu Chah Nulth, and Europe; dotted lines are used for mismatch distributions of Middle East, !Kung, and Africa; solid lines are used for intermatch distributions. The right-hand panel is based on high-resolution mtDNA restriction site data, and the other panels are based on mtDNA sequence data from hypervariable region I. Redrawn from Figures 3 and 6 of Harpending et al. (1993).

population expands and subdivides at the same time, as the replacement hypothesis assumes. The pattern seems consistent with two alternative scenarios.

The first scenario assumes that about 100,000 years ago an initial randomly mating population separated into several groups that may have been completely isolated from each other and were at most weakly connected by gene flow. This initial separation event gave rise to the leading intermatch wave in the center panel of Figure 5. About 50,000 years later the groups underwent simultaneous bottlenecks or expansions in size, producing the within-population mismatch waves. This scenario is a weakened form of the replacement or Garden of Eden hypothesis and is obtained by relaxing the conventional assumption that the separation and the expansion were simultaneous. For this reason Harpending et al. (1993) refer to it as the *weak* Garden of Eden hypothesis.

The leading intermatch wave is also consistent with a second scenario, which also assumes that the groups expand simultaneously but does not assume any initial separation event. Instead, the population is subdivided as far back into the past as we care to look. It is crucial that the groups be only weakly connected by gene flow. As we look backward from the present, weak gene flow implies that the sample from each group may coalesce to a single lineage before any migrations occur. Then, no additional coalescent events are possible until migration moves one of these lineages to another group. Because gene flow is weak, this may take a long time. When a migration finally occurs, the next coalescent event will join all the samples from one group to all the samples

in another, thus producing an intermatch wave. This intermatch wave leads the mismatch waves because of the time that elapses before a migration occurs. Because this elapsed time is a random variable with no bearing on any expansion, separation, or other population-level event, the leading intermatch wave does not date any such event. It tells us only that before the expansions documented by the mismatch waves, the population was subdivided, with weak gene flow between subdivisions. We refer to this as the divided Eden hypothesis.

Harpending et al. (1993) performed extensive simulations showing that leading intermatch waves occur frequently when the pre-expansion population is subdivided and only weakly connected by gene flow. Thus there is good reason to believe that the major human populations separated long before the expansions that are reflected in the within-group waves. Harpending et al. (1993) did not, however, distinguish between the two scenarios just outlined.

In choosing between these scenarios, we rely on the confidence regions that Rogers (1994b) calculated under various models of population structure. When the initial population is structured, as in the multiregional and divided Eden hypotheses, the confidence region allows an initial population of only 1500 breeding females. This is clearly too few to populate Europe, Africa, and Asia and thus refutes the strong form of the multiregional hypothesis. Harpending et al. (1993) showed that under the divided Eden hypothesis the intermatch wave is unlikely to lead the mismatch waves by a margin as large as that in the data unless the subpopulations exchange fewer than 0.5 migrant per generation. This implies a far greater level of between-group variation than has ever been seen in modern human populations of this size.[4] This observation is not conclusive, because the ancient population may have had a pattern of gene flow unlike that of any modern population. Nonetheless, it provides grounds for skepticism toward the divided Eden hypothesis.

This leads us toward the alternative—the weak Garden of Eden hypothesis. But this hypothesis encounters a problem too, because it also stipulates that the pre-expansion population was highly structured, and we just argued that this seems unlikely. There would be no difficulty, however, if the "expansion" that is dated by the confidence regions referred not to the within-group expansions of the weak Garden of Eden hypothesis but to the earlier separation event. Under this interpretation, the "pre-expansion" population whose size is so small is the same as the preseparation population of the weak Garden of Eden hypothesis.

But does this interpretation make sense? The confidence regions were obtained from a single mismatch distribution calculated from a worldwide sample; let us refer to this as the pooled mismatch distribution. When a population splits into several subdivisions, its effective size increases even if its census size does not (Nei and Takahata 1993).

Therefore the separation event that is posited by the weak Garden of Eden hypothesis would generate a wave in the pooled mismatch distribution. The weak Garden of Eden hypothesis also posits that several tens of thousands of years later each subpopulation undergoes a bottleneck or episode of growth. These later events would have profound effects on within-group mismatch distributions but no effect on the intermatch distributions. The pooled distribution is an average of K within-group mismatch distributions, and $K(K-1)/2$ intermatch distributions, where K is the number of groups. If K is large, then within-group distributions will have only a small effect on the pooled distribution. Consequently, the wave in the pooled distribution should date the separation, with a downward bias that is small when the number of groups is large.

To test this idea, we simulated data under the weak Garden of Eden hypothesis. Each simulation begins with a randomly mating population at mutation-drift equilibrium with $\theta = 1$. At 14 mutational time units before the present this population grows by a factor of 10 and simultaneously splits into 25 subpopulations, which exchange 0.1 migrant per generation. Things are constant for 7 mutational time units, after which each subpopulation grows again by a factor of 50. Using this model of population history, we simulated 1000 pooled mismatch distributions and used Rogers's (1994a) method to estimate τ from each. The median estimate of τ is 12.74—much closer to the separation time of 14 than to the major episode of growth at time 7. Thus, under the weak Garden of Eden hypothesis with 25 groups, the pooled distribution provides an estimate of the separation time with a modest downward bias.

When the number of groups is 3 rather than 25, the downward bias is much larger. But because continental populations do not mate at random, the effective number of groups is much larger than the number of continents, and the three-subdivision result should not apply. Consequently, if the weak Garden of Eden hypothesis is correct, then the confidence regions provide a somewhat biased estimate of the time of separation. The small estimates of initial population size refer to the preseparation population of the weak Garden of Eden hypothesis.

Selection Hypothesis

So far, we have assumed that mtDNA evolution is selectively neutral, yet this may not be so. Suppose that a favorable mtDNA mutation occurred 50,000 years ago and swept through the population. This would produce a wave like that in Figure 2. Our estimates would then refer not to the size of the human population but to the size of an expanding clade of superior mutants. Our time estimate would refer to the time of this selective sweep of the new allele through the population.

The selection hypothesis receives apparent support from two studies that show that variation in mtDNA is inconsistent with a model of neutral evolution (Excoffier 1990; Merriwether et al. 1991). However, the hypothesis that the studies reject assumes not only that the mtDNA is neutral but also that the population size has always been constant. Thus the pattern that these studies identify may have been caused by population growth rather than by selection.

We know of two ways to evaluate the selection hypothesis. First, Harpending et al. (1993, p. 495) point out that this hypothesis is inconsistent with patterns such as that in the center panel of Figure 5. Once an advantageous mutation becomes fixed in the population, all mitochondria will trace their ancestry back to the original advantageous mutant. Consequently, as an advantageous mutation sweeps through a population, it erases any earlier mismatch and intermatch waves. Thus the leading intermatch wave in the center panel of Figure 5 implies that neither the !Kung nor the Nuu Chah Nulth wave could have been caused by an advantageous mutation. Second, if the wave in the human data is due to an environmental catastrophe, such as a glaciation or the Toba volcanic supereruption that we discuss later (Rampino and Self 1992), then it should have affected other species in addition to our own. The mismatch distributions of other species should show waves similar to those in the human data. Figure 6 shows that the mismatch distributions of humans and of Eastern Chimpanzees do indeed have waves at about the same place. Although either wave could have been produced by the advance of a favorable mutation, it is unlikely that this would occur in both species at the same time. Thus this evidence supports the hypothesis that the mismatch waves reflect changes in population size rather than natural selection. It also suggests that the waves of both species reflect some environmental catastrophe.

Arguments against a Bottleneck

The preceding sections suggest that bottlenecks, or expansions from small size, occur in the histories of most human populations and also in that of the human population as a whole. This conclusion appears to contradict several studies that argue that no narrow bottleneck has occurred in the past million years or so. In what follows we argue in two cases that, in fact, no contradiction exists and in a third case that the argument against an expansion is flawed.

Polymorphism at the Apolipoprotein C-II Deficiency Allele. Xiong et al. (1991) studied a polymorphism at the apolipoprotein C-II deficiency allele, which causes lipoprotein abnormalities that are severe in

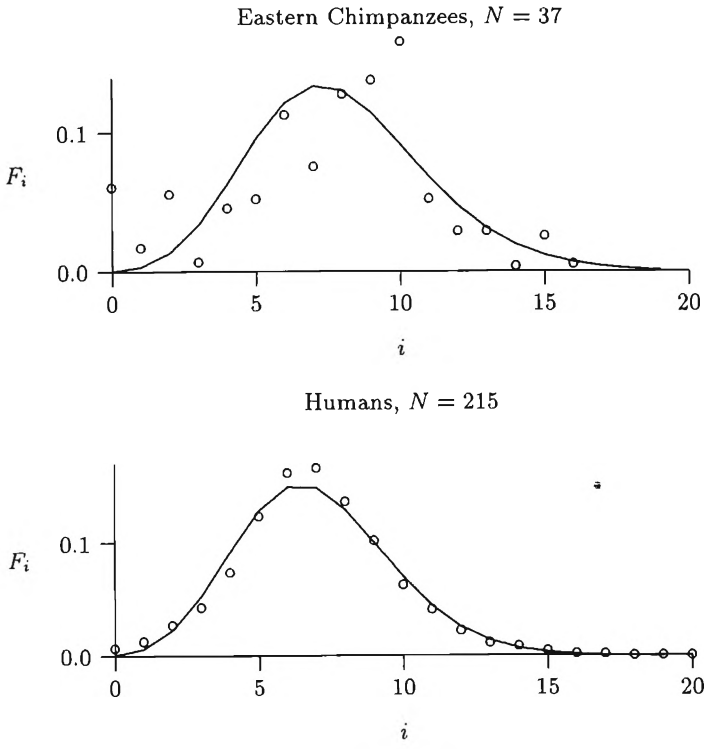

Figure 6. Eastern Chimpanzee (*Pan troglodytes schweinfurthii*) and human mismatch distributions. The mismatch distributions of both species are based on 245 homologous nucleotides from the mtDNA control region. Solid lines show theoretical distributions fitted by method of moments after constraining $F_0 = 0$, as described by Rogers (1994a). Source of chimpanzee data: P. Morin and H. Harpending (unpublished data, 1994). Source of human data: S. Sherry, H. Soodyall, L. Vigilant, and M. Stoneking (unpublished data, 1994).

affected homozygotes and mild in heterozygotes. Two variants of the allele have been found, one from Japan and the other from Venezuela. The pattern of similarities between the two variants suggests that they are descended from a common ancestor who lived at least 500,000 years (or about 20,000 generations) ago. This seems remarkable. The allele is, after all, deleterious. How could it have survived so long in the face of selection?

To find out, Xiong et al. (1991) calculated the expected value $\bar{t}_0$ of the number of generations that a deleterious allele will persist in a population. This result depends on the effective (male plus female) population size N_e, on the initial allele frequency p, and on the coefficients of selection h and s against heterozygotes and affected homozygotes,

Table 1. Mean Persistence Time of a Deleterious Allele

N_e	p	h	s	$\bar{t}_0$ (Generations)
250	0.00400	0.000	0.05	8.6
500	0.00400	0.000	0.05	15.8
1,000	0.00400	0.000	0.05	29.0
1,000	0.00100	0.000	0.05	9.5
1,000	0.00100	−0.005	0.05	11.0
1,000	0.00100	−0.010	0.05	13.1
5,000,000	0.00100	0.000	0.05	12,146.0
500,000	0.00001	−0.002	0.10	3.3×10^5
10,000	0.00400	−0.005	0.05	2,401.4
10,000	0.00400	−0.001	0.05	248.3
10,000	0.00400	0.000	0.05	210.0
10,000	0.00400	0.001	0.05	170.8

The calculations assume a population of size N in which the relative fitness of heterozygotes is $1 - h$, whereas that of affected homozygotes is $1 - s$. The initial frequency of the deficiency allele is p, and the expected time (in generations) during which it persists in the population is $\bar{t}_0$. Calculations are based on Eqs. (15a), (16), and (17) of Li and Nei (1972). The upper portion of the table is taken from Xiong et al. (1991).

respectively. Xiong et al.'s results are shown in the upper portion of Table 1. Notice that $\bar{t}_0$ is much less than 20,000 (the observed persistence time) in all the rows where $N_e \leq 1000$. On this basis Xiong et al. (1991) rejected the hypothesis that $N_e \leq 1000$.

However, we are interested in a somewhat different hypothesis. As discussed, analysis of mismatch distributions indicates that the human population survived a period during which it had about 5000 females, or 10,000 individuals. We repeated the calculations of Xiong et al. (1991) for this population size, and our results are shown in the lower portion of Table 1. Those results show that even when $h = 0$ (no heterozygote advantage), this population size makes the expected persistence time 250 generations, or 6250 years. Thus these data cannot reject a bottleneck in which $N_e = 10{,}000$ for 6250 years. And this statement is still too conservative, because 6250 years is only the mean persistence time. To reject the hypothesis that $N_e = 10{,}000$ for a period of T years, we would need to show that the probability of persistence longer than T is less than some significance level, such as 0.05. The values of T that cannot be rejected would constitute a 95% confidence interval. We do not know the extent of this confidence interval, but it surely includes values larger than the mean (i.e., 6250 years). Thus there is no contradiction between the apolipoprotein data and the mtDNA mismatch data.

HLA Polymorphism. A similar case against narrow bottlenecks has been made using evidence from HLA polymorphisms. Several of these

polymorphisms are shared by humans and chimpanzees and are thus at least 4×10^6 years old. From this evidence Takahata (1990, 1993a,b) has shown that the total (male plus female) human population probably did not drop below 10,000 individuals for any extended period during the Pleistocene. These results are consistent with the mtDNA mismatch data, which imply a female population of about 5000.

Templeton's Analysis of mtDNA. Templeton (1993) has also studied human mtDNA data and reports evidence of isolation by distance at all levels of the genealogical tree. At lower levels of the cladogram, corresponding to the past 30,000 years, isolation by distance is to be expected under all models of modern human origins. To refute either the replacement or the weak Garden of Eden hypothesis, one must show that the pattern of isolation by distance extends back beyond (say) 100,000 years B.P. Although Templeton does not provide such a date, he does report evidence for isolation by distance even at the highest levels of his cladogram, suggesting that the pattern extends well back into the Pleistocene. We mistrust this inference because, as explained later, we doubt that high-level clades can be accurately identified.

Templeton (1993) also reports evidence of two local geographic expansions (one in Europe and the other in the Middle East and northern Africa) but no evidence of any global geographic expansion. This appears to contradict the mismatch distributions, which support an expansion. Yet there is really no contradiction. Templeton is concerned with an increase in the population's geographic extent, whereas the mismatch evidence refers to an increase in the number of individuals. If the population grew without colonizing new territory, then both inferences could be correct. This interpretation is supported by Templeton's subsequent research, which indicates an expansion in population size (A. Templeton, personal communication, 1993).

Nonetheless, Templeton's result would appear to restrict severely the hypotheses that we can plausibly entertain about modern human origins. As Templeton emphasizes, it appears to refute the replacement hypothesis, which requires an expansion in geographic extent as well as in numbers. Templeton's result is similarly inconsistent with the weak Garden of Eden hypothesis, which also traces the human species back to a single small population about 100,000 years ago. We are skeptical, however, of Templeton's analysis.

Templeton's method for detecting geographic expansions is based on the premise that when an expansion occurs, "one or more younger clades should have significantly larger geographical distribution than some older clades" (Templeton 1993, p. 63). The rationale for this premise is twofold. First, when a population expands into a new area, the expanding population may not include all the clades present in the parent pop-

ulation. When this happens, the expansion will increase the geographic extent of some clades while leaving that of others unchanged. Second, if a mutation occurs during a geographic expansion, the clade comprising its descendants may become widely dispersed. For both reasons geographic expansions may cause some younger clades to occupy more territory than some older clades.

We grant that geographic expansions may have this effect but are not convinced that they always do so. For example, suppose that the size expansion in Figure 1 were accompanied by a geographic expansion. If the entire population participates in the expansion—a realistic possibility because our initial population is small—then no older clades would be left behind. No mutations would arise during our hypothetical expansion because its duration is so short. Consequently (and contrary to Templeton's expectation), no younger clades would exceed older clades in geographic extent. Templeton's argument fails whenever the expanding population contains all the mtDNA clades of the parent population and the expansion takes place too rapidly for new mutations to arise. However, the expansion in Figure 1 is unrealistically brief (being instantaneous). Had the expansion lasted 1000 years, mutations would have arisen within its duration. Thus Templeton's argument may be correct. As yet, however, the case in its favor does not seem solid enough to serve as a basis for statistical inference.

In addition, we are skeptical of the statistical method that implements this idea. To compare the geographic extents of younger and older clades, one must first determine their ages. This determination need not be precise but must provide some information. Templeton (1993) obtains this information by using genetic data to link haplotypes together as a cladogram, or unrooted tree. Haplotypes near the tips of the cladogram are assumed to be younger on average than those in the interior. This procedure should work well when the coalescent events are well separated in time but would fail with data such as those in Figure 1. As discussed, only 7 mutations are available for dating the 37 clades that antedate the expansion. Consequently, no statistical method could tell us much about the ages of these clades. And such data are exactly what we should expect when a population has expanded in size.

Templeton and Sing (1993) consider four sources of uncertainty regarding their estimated cladogram and conclude that their inferences are robust with respect to all four. They do not, however, consider the problem raised here. We conclude that Templeton's method is unlikely to work well in populations that have expanded rapidly in size, and we are therefore skeptical of the conclusion that no global range expansion has occurred.

Equilibria and Convergence

We are now in a position to compare the mismatch analysis with other forms of genetic evidence. In several places we will encounter alternative interpretations. To choose among them, we must calculate not only the evolutionary equilibrium value but also the rate at which this equilibrium is approached. Before proceeding, therefore, we interrupt our review with a digression that introduces these concepts.

If demographic parameters remain constant, each of the statistics considered will eventually reach some equilibrium value at which it ceases to change. The various statistics differ in the rates at which they converge toward their equilibria. We illustrate these ideas using a variable that has figured prominently in discussions about modern human origins: the mean number m of mtDNA nucleotide site differences between pairs of individuals within a population.

The equilibrium value of m is equal to

$$\theta \equiv 2N_{eF}u, \tag{4}$$

where u is the aggregate mutation rate over the portion of the mitochondrial genome that has been sampled and N_{eF} is the effective female population size.[5] So long as N_{eF} remains constant, m will move closer and closer to its equilibrium θ. Because θ is proportional to population size, reductions in population size will cause reductions in m, and vice versa. This is one of the reasons why m provides information about population history.

The other reason follows from an asymmetry in m's rate of change. It takes N_{eF} ln 2 generations for m to move halfway from any initial point to its equilibrium. In other words, N_{eF} ln 2 is the half-life of the process by which m converges toward equilibrium.[6] When the population is small, the half-life is short and convergence is therefore rapid. But when the population is large, the half-life is long and m's convergence is therefore slow.

The significance of this asymmetry is illustrated in Figure 7. The upper graphs show hypothetical time paths of female population size. Before the bottleneck at generation 5000, the population is large and m is at its equilibrium value of $\theta = 100$. To make the discussion concrete, we assume, as before, that the mutation rate is $u = 0.0015$. This implies that $N_{eF} = \theta/(2u) = 33{,}333$ before the bottleneck. Then, at generation 5000 the population crashes to 33 females and m's equilibrium value becomes $\theta = 0.1$. Convergence toward this new equilibrium is rapid because the half-life ($33 \times \ln 2 \approx 23$ generations) is short. The two panels on the left-hand side of Figure 7 illustrate the effect of a long bottleneck, which lasts 333 generations, or 14.6 half-lives. During 14.6

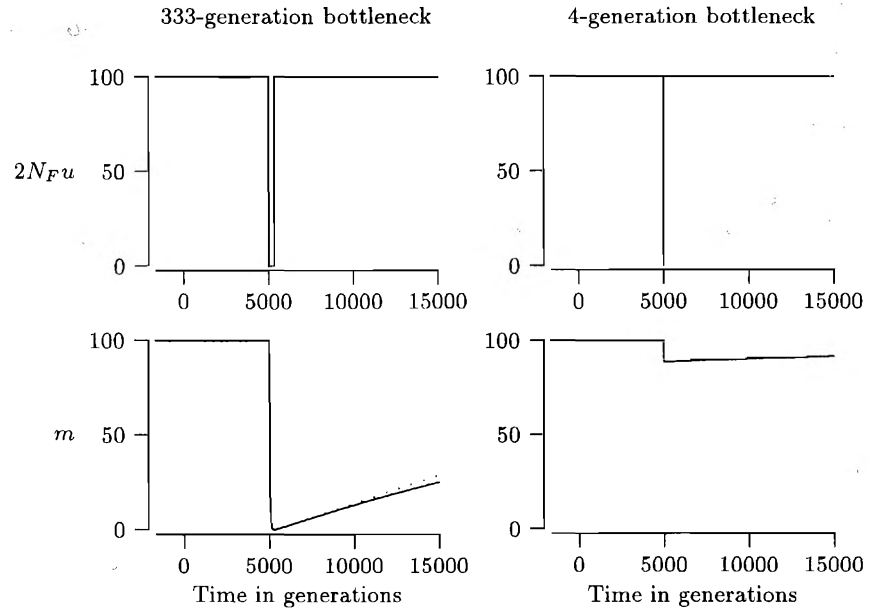

Figure 7. Effect of a bottleneck on m, the mean pairwise difference. The mean pairwise difference m is calculated using the equation in note 6. In both cases the bottleneck population is 1/1000 as large as the original population.

half-lives the difference between m and θ is reduced to a fraction $0.5^{14.6}$ = 0.00004 of the original difference. As Figure 7 confirms, convergence is nearly complete. The two panels on the right-hand side of the figure describe a brief bottleneck of only 4 generations, or 0.17 half-life. During the brief bottleneck, the difference between m and θ is reduced to a fraction $0.5^{0.17}$ = 0.89 of the original difference. Thus the brief bottleneck produces only a small change in m's value. To have a large effect, a bottleneck must last on the order of a half-life. The half-life tells us which demographic perturbations will be reflected in genetic statistics and which will not.

In Figure 7 m's rapid fall during the bottleneck stands in stark contrast to its gradual rise after the bottleneck ends. m will eventually level off at its old value, but that will take well over a million years. Consequently, the reduction in m's value that was produced by the bottleneck will be evident for an exceedingly long time. This is also a consequence of m's half-life: After the bottleneck the population is large and the half-life is 23,105 generations—nearly 600,000 years. Convergence following a bottleneck is therefore much slower than convergence during a bottleneck. Were this not the case—were it true, for example, that m's

rise were as rapid as its fall—m would be of little use to students of demographic history. The effect of a bottleneck would quickly disappear, and m could inform us only about the recent past.

These comments apply not only to m but to any genetic statistic that converges geometrically to an equilibrium. Statistics that converge too slowly are little affected by demographic perturbations and therefore cannot tell us much about them. On the other hand, statistics that converge too quickly cannot reach very far into the past. For both reasons rates of convergence play a central role in the sections that follow.

Mitochondrial Diversity of the Human Population

The human species is remarkably low in mitochondrial genetic diversity. At equilibrium the diversity of selectively neutral genes should be low in small populations and high in large ones. Molecular assays confirm that human mitochondrial diversity is indeed lower than that of more numerous species such as *Drosophila melanogaster* (Li and Sadler 1991; Jorde et al. 1994). However, our diversity is also lower than that of the anthropoid apes, whose populations are much smaller (Ferris et al. 1981; Wilson et al. 1985; Kocher and Wilson 1991). This puzzling discrepancy is illustrated in Table 2, which compares rates of nucleotide substitution in the mtDNA of humans and chimpanzees. Here, diversity within populations is measured by a statistic that is approximately equal to the mean pairwise difference m divided by the number of nucleotide sites sampled. Because of its close relationship to m, this statistic converges at the same rate. The data sets in the table were chosen for comparison because they deal with essentially the same portion of the mitochondrial genome and use similar statistics to estimate the substitution rate.

The chimpanzee numbers are obviously larger than the human ones. To summarize this difference, we calculate the expected number of substitutions per site between a random pair of individuals, each drawn with equal probability from one of the three major populations. Table 2 implies that this number is 0.11 for chimpanzees and 0.017 for humans.[7] Thus chimpanzee mitochondrial diversity exceeds that of humans by nearly an order of magnitude. Orangutan mitochondrial diversity exceeds that of humans by an even larger margin (Ferris et al. 1981).

Why is the mitochondrial diversity of our species so low despite our relatively large population? The answer depends on whether or not gene diversity is at equilibrium. At equilibrium between mutation and genetic drift a random pair of individuals should differ at a fraction $2N_{eF}\mu$ of mitochondrial nucleotide sites, where N_{eF} is the number of females and μ is the mutation rate per site per generation [Nei 1987, Eq. (10.8)].

Table 2. Mean Numbers of Mitochondrial D-Loop Nucleotide Substitutions between Pairs of Individuals Within and Between Populations

	Human Races[a]		
	Caucasoid (N = 20)	*Mongoloid* (N = 71)	*Negroid* (N = 10)
Caucasoid	**0.0094**	0.0012	0.0028
Mongoloid	0.0128	**0.0137**	0.0015
Negroid	0.0194	0.0203	**0.0238**

	Chimpanzee Subspecies[b]		
	Pan troglodytes schweinfurthii (N = 40)	*Pan troglodytes troglodytes* (N = 18)	*Pan troglodytes verus* (N = 8)
Pan troglodytes schweinfurthii	**0.029**	0.030	0.137
Pan troglodytes troglodytes	0.072	**0.055**	0.087
Pan troglodytes verus	0.192	0.155	**0.081**

Boldfaced diagonal entries estimate the mean number of substitutions per nucleotide site between pairs of individuals within populations. Entries below the diagonal estimate this quantity for pairs from different populations. Entries above the diagonal give between-group substitutions minus the mean of the two corresponding within-group values [Nei 1987, Eq. (10.21)].

a. Horai and Hayasaka (1990).

b. Morin et al. (1993).

Setting $2N_{eF}\mu$ equal to the observed value 0.017 and substituting $\mu = 4.1 \times 10^{-6}$ (Ward et al. 1991) gives $N_{eF} \approx 2000$. Several researchers have obtained $N_{eF} \approx 5000$ by means of similar calculations (Nei and Graur 1984; Chakraborty et al. 1987; Bowcock et al. 1991; Maynard Smith 1990). Thus our low genetic diversity is consistent with a long-term human population size of only a few thousand females, or perhaps 10,000 individuals in all.

However, we have already seen that this equilibrium is approached only slowly, with a half-life of N_{eF} ln 2 generations. For a female population of 10,000 the half-life would be 6900 generations, or 170,000 years. A larger population is more reasonable and implies even slower convergence. Yet we have already seen that the mtDNA mismatch data imply that the human population expanded from a small beginning within the past 150,000 years. Consequently, not enough time has elapsed for m to reach equilibrium. Thus m's low value must reflect some historical event, such as a bottleneck in population size, rather than a long history of moderate population size (Haigh and Maynard Smith 1972; Brown 1980; Jones and Rouhani 1986; Wills 1990). This hypothesis is perfectly consistent with the mtDNA mismatch data.

Greater Mitochondrial Diversity in Africa

Thus far, estimates of mitochondrial diversity have always been larger within Africa than within other major continental populations (Cann et al. 1987; Vigilant et al. 1989, 1991; Bowcock et al. 1991; Horai et al. 1993; Jorde et al. 1994). Some researchers infer from this that the African population is older and therefore the likely point of origin if the replacement hypothesis is correct (Stoneking 1993). It is not clear, however, that this pattern is statistically significant. Although Africa is significantly more diverse in microsatellite polymorphisms (Bowcock et al. 1994, Table 2), no study has yet demonstrated a significant excess in African mitochondrial diversity (Templeton 1993). We will not pursue that controversy here, however, because we believe it to be irrelevant: Even if we knew beyond doubt that African diversity was greater, it would not follow that Africa is the point of origin.

Why Genetic Diversity Does Not Measure a Population's Age. Aoki and Shida (1993) recently used computer simulations to argue that a population's genetic diversity does not measure its age. Their simulations begin with an ancestral population, some members of which colonize a new area to form a second population, which in turn gives rise to a third population. In the simulations there was no tendency for the ancestral population to end up with greater genetic diversity. However, the simulations assumed that no bottlenecks in population size occurred when new populations were founded. Aoki and Shida's result may be an artifact of this possibly unrealistic assumption. Therefore we support their conclusion with a different argument, which begins by considering why the genetic diversity of a population can be construed as a measure of age.

Diversity can be measured by the mean number m of nucleotide differences between pairs of individuals within a population. Recall from Figure 7 that after a severe and prolonged bottleneck, m, rises approximately linearly from a point near zero. For thousands of generations after this bottleneck m is approximately $2u$ times the number of generations since the bottleneck. In other words, m measures the postbottleneck time in units of $1/(2u)$ generations. This is the only sense in which m can be construed as a measure of population age.

However, the extended bottleneck in Figure 7 is remarkable both for its severity and for its duration: The population is reduced to 33 females for a period of 333 generations or 8333 years. If the bottleneck were brief, such as the four-generation bottleneck in the figure, then m would be only modestly reduced and therefore would not measure age. m measures population age only if there has been a prolonged, severe bottleneck.

What makes this view unpalatable is the extreme severity and duration of the bottleneck it requires. It takes five half-lives to reduce m 97% of the way to its equilibrium. This requires 4300 years with a population of 50 females, or 433 years with a population of 5. Because this seems preposterous, we agree with Aoki and Shida (1993) that genetic diversity should not be interpreted as a measure of population age. Nei and Ota (1991) arrive at the same conclusion using a different argument.

What *Do* Race Differences in Diversity Mean? Although the greater diversity of African mtDNA may yet turn out to be a sampling artifact, let us set this issue aside and ask what the excess would mean if it were real. We have already argued that it should not be interpreted as a measure of the population's age. If not age, then what? As before, we must consider both equilibrium and nonequilibrium hypotheses. As we have seen, $m = 2\ n_{eF}u$ at equilibrium, where n_{eF} represents a continental effective female population size. Under a hypothesis of equilibrium with no gene flow, therefore, the greater African diversity would imply that the African population has long been larger than those of Europe and Asia. Gene flow complicates the picture: Greater African diversity might also reflect greater gene flow into Africa than into Europe and Asia. However, this is inconsistent with the large genetic distance between African and non-African populations (see the later section "Trees Based on Nuclear DNA"). Thus the hypothesis of equilibrium implies that the African population was larger.

We have also seen that in the absence of gene flow the value of m within each continental population converges to its equilibrium with a half-life of n_{eF} ln 2 generations. With gene flow, the effective size of each continental population is larger and convergence should be even slower. Thus the half-life must be at least n_{eF} ln 2. The mtDNA mismatch data imply that the global effective population size after the expansion was at least 150,000 females, so the 3 continental populations must have included at least 50,000 females each. Thus the half-life is at least 35,000 years, and as many 3 half-lives may have passed since the proposed expansion.[8] This is long enough for m to move seven-eighths of the way from its initial value to its equilibrium. Thus it is plausible to suppose that the African excess in mitochondrial diversity may reflect a larger population size. But because this conclusion was reached using assumptions that made m's half-life as small as possible, a variety of nonequilibrium interpretations are also plausible. Greater African diversity might reflect a less recent bottleneck or one less severe than those suffered by other continents. It might reflect an ancient pattern of gene flow. We see no way to choose between these alternatives.

Genetic Differences between Human Races

Magnitude. Population history is written not only in genetic differences within populations but also in the differences between them. Consider, for example, the upper portion of Table 2, which measures the amount by which individuals of different races differ over and above within-race differences. The average of the three entries above the diagonal is 0.0018 for humans and roughly 46 times this value for chimpanzees. Human race differences are remarkably small.

This estimate is based on mtDNA, which evolves as a single locus. We may gain more insight by aggregating over numerous loci, using nuclear DNA. With such data, group differences are generally measured using Wright's (1951) F_{ST}, the ratio of genetic variance among groups to the variance between random genes drawn from the population as a whole. Several studies of nuclear polymorphisms have found that $F_{ST} \approx 0.1$ for the human races (Wright 1978; Nei and Roychoudhury 1982; Bowcock et al. 1991, 1987; Jorde et al. 1994), and the same result has also been obtained from craniometric data (Relethford and Harpending 1994). For mtDNA, $F_{ST} \approx 0.3$ (Stoneking et al. 1990; Merriwether et al. 1991). The difference between these two estimates is exactly as would be predicted from the observation that, because mtDNA is maternally inherited, its population size is one-fourth that of nuclear DNA (Takahata 1991, pp. 593–594).

Hypothesis of Migration-Drift Equilibrium. But what do these estimates mean? The answer depends on whether the human races have been in place long enough to reach equilibrium between the effects of migration and genetic drift. Let us assume for the moment that they are at equilibrium. This assumption implies that the value of F_{ST} depends on the amount and pattern of interracial migration. At equilibrium

$$F_{ST} = \frac{1}{1 + 4nm_eK/(K-1)}, \tag{5}$$

where n is the effective number of (male and female) individuals within each of K races and m_e is the effective migration rate (Rogers and Harpending 1986, p. 1317). By setting Eq. (5) equal to 0.1 (the observed F_{ST}) and assuming that three races of equal size exchange migrants at a common rate m, we find that the number nm of migrants per generation between each pair of groups is almost exactly 1, in agreement with Takahata (1993b, p. 18).[9] Our answer differs from analogous results derived elsewhere[10] because in our model the number of races is three instead of infinite. The answer tells us what is implied by F_{ST} under the hypothesis of migration-drift equilibrium: The racial populations must have exchanged approximately one migrant per generation. With this level of

Table 3. Half-Life of Convergence of F_{ST} under Island Model Migration

N	*Generations*	*Years*
1,000	77	1,916
10,000	768	19,203
100,000	7,534	188,347
1,000,000	63,013	1,575,329

The island model assumes equal rates of migration between the three pairs of continental populations. The half-life is calculated as $-(\ln 2)/\{2 \ln[(1 - s)(1 - 3m/2)]\}$ (Rogers and Harpending 1986, p. 1322).

migration, strong selection would be needed to account for the substantial race differences that are observed in some characters (Takahata 1993b, p. 18).

Hypothesis That We Are Not at Equilibrium. Before evaluating the hypothesis of migration-drift equilibrium, we ask the opposite question: What would the observed value of F_{ST} imply if the human races were not at equilibrium? In populations that have been completely isolated for t generations [Wright 1969, Eq. (13.5)]

$$F_{ST} \approx 1 - \exp(-t/2n), \tag{6}$$

where n is the effective (male and female) size of each racial population. The weak Garden of Eden hypothesis indicates that the human races have been separate for roughly 100,000 years, or $t \approx 4000$ generations. If so, then the estimate that $F_{ST} = 0.1$ implies that $n \approx 20{,}000$, which is in reasonable agreement with a similar calculation by Bowcock et al. (1991, p. 842). With migration, n would have to be smaller to achieve the observed value of F_{ST}. Thus, if human racial differences are not at equilibrium, then $n < 20{,}000$. This places an upper bound on the effective racial population size under the hypothesis that the human races are not at migration-drift equilibrium. We hasten to add, however, that this bound on racial population sizes refers to the effective population size (Crow and Kimura 1970) and may be much smaller than the mean population size.

Which Hypothesis Is More Plausible? The answer to which hypothesis is more plausible depends both on what we believe about the origin of modern humans and on the rate at which F_{ST} converges toward its equilibrium. The rate of convergence depends on population size, as shown in Table 3. The table assumes equal rates of migration between the three continental populations, an unrealistic assumption that will make

the half-life values smaller than they should be.[11] Thus the values in the table provide minimum bounds on the true half-life.

Using this minimum bound, we calculate that the half-life of F_{ST} in years is roughly twice the total population size. Because the mtDNA mismatch data imply a total population size of at least 300,000, the half-life of F_{ST} cannot be less than 600,000 years. With unequal rates of migration between the continents, the half-life would be even larger. Either way, migration-drift equilibrium could not have been reached in the 70,000 years since the proposed expansion. Consequently, the non-equilibrium interpretation of F_{ST} should apply, and it tells us that $n <$ 20,000, where n is the effective (male and female) racial population size.

What does this imply about the effective size of the total human population? Assuming that there are three races, one might suppose that the total effective size would be $3n < 60{,}000$. However, population structure inflates the effective size. Nei and Takahata (1993) show that the effective size is

$$N_e = \frac{N}{1 - F_{ST}}, \tag{7}$$

where N is the sum of the effective sizes of the subpopulations. Thus the effective size of the total population, including all three races, is less than $3n/(1 - F_{ST}) \approx 66{,}000$. This presents a dilemma: The premise that $N_e > 300{,}000$ leads to the conclusion that $N_e < 66{,}000$!

We see only one way to resolve this contradiction: At some time after their separation the racial populations must have been small. During this interval, genetic race differences would have accumulated rapidly. Then, subsequent population growth would have frozen these differences by greatly reducing the rate of genetic drift. Under this hypothesis the 300,000 and 66,000 estimates refer to different things: The estimate that $N_e < 66{,}000$ refers to the effective size over the entire period since the races separated and includes the initial period of small racial population sizes. On the other hand, the estimate that $N_e > 300{,}000$ refers only to the period since the races grew large. This inference dovetails nicely with the weak Garden of Eden hypothesis, which also holds that the racial populations separated long before their expansion. The F_{ST} data allow us to infer, in addition, that the racial populations were relatively small during this interval.

Trees Based on Nuclear DNA

The problem of modern human origins has also been addressed using trees inferred from nuclear DNA. With nuclear DNA the tree that relates the individuals in a sample will differ from locus to locus. Con-

sequently, one cannot describe relationships among individuals with any single tree. Instead, the aim is to infer a tree that describes relationships among whole populations.

This approach has several advantages over trees based on mtDNA. First, relationships among populations are more interesting than those among individuals. Second, the fact that each locus has its own tree means that the more loci one studies, the better will be the estimates of parameters describing population history. This does not happen with mtDNA because there is only one mtDNA tree and it contains only a limited amount of information (Nei and Roychoudhury 1993).

The most recent trees for the major human populations are those of Cavalli-Sforza et al. (1988) and Nei and Roychoudhury (1993). In both trees the deepest split separates African populations from all others. In Nei and Rouchoudhury's tree the next deepest split separates Europeans and Indians from Asians, Australians, and Amerindians. These major branches are probably not statistical artifacts because they are strongly supported by bootstrap analysis. However; there are three sources of ambiguity about what these branches mean.

The first should be familiar by now: Genetic race differences may or may not be at migration-drift equilibrium. If they are at equilibrium, then the deep split between African and non-African populations would reflect a low rate of gene flow across the Sahara Desert (Imaizumi et al. 1973), whereas the split separating Europeans and Indians from Asians would reflect a low rate of gene flow across the Himalayas. On the other hand, if we are not at equilibrium, then the trees must be telling us about history.

We encounter a second source of ambiguity if we decide in favor of the nonequilibrium interpretation. This implies that the tree tells us about history but still leaves us in doubt about the sort of historical events that are involved. They could either be population fissions or ancient patterns of gene flow. We return to this second source of ambiguity later.

We can resolve the first source of ambiguity by calculating half-lives. Trees inferred from nuclear DNA are generally based on some kind of genetic distance statistic. Some measures of genetic distance converge at the same rate as F_{ST} (Harpending and Jenkins 1973; Harpending and Ward 1982). The other measures are closely related and probably converge at similar rates. Thus the half-lives calculated in Table 3 should also apply to genetic distances. As we have seen, mtDNA mismatch distributions indicate that the human races separated relatively recently and that their populations have subsequently been large. For this reason, we favor the nonequilibrium interpretation of genetic distance trees.

This still leaves us with two plausible interpretations: First, the trees may record the history of population fissions. If so, the trees imply that African and non-African populations separated early in human evolution,

whereas Asians and Europeans separated somewhat later. This pattern is often interpreted as evidence for an African origin of modern humans, but it seems equally consistent with any number of other scenarios. For example, Africa could have been colonized by emigrants from Asia, and Europe could have been colonized from the same source 10,000 years later. Our uncertainty on this point constitutes the third source of ambiguity in the interpretation of human population trees.

Returning to the second source of ambiguity, it is also possible that the trees reflect ancient patterns of gene flow rather than population fissions. This view receives support from the weak Garden of Eden hypothesis and also from the F_{ST} data that imply a period of small racial population sizes. If the races remained small and partially isolated for tens of thousands of years after their separation, then they could have reached migration-drift equilibrium relatively rapidly. Subsequent population growth would have frozen this ancient equilibrium. If so, then trees inferred from nuclear DNA may reflect patterns of gene flow before the expansion.

The Age of "Eve," Our Common Mitochondrial Ancestor

Finally, we turn to the form of evidence that has received the most attention in the popular press. Our common mitochondrial ancestor is whimsically referred to as Eve, and much of the literature on modern human origins revolves around estimates of her age. Several studies have estimated that she lived within the past 250,000 years (Cann et al. 1987; Vigilant et al. 1989, 1991; Hasegawa and Horai 1991; Denaro et al. 1981; Excoffier and Langaney 1989). This result has been offered as evidence against the multiregional hypothesis (Stoneking 1993). Although this estimate has been challenged on statistical grounds (Nei 1992; Templeton 1993), it is supported by more recent research using new data and improved methods (Hasegawa et al. 1993; Tamura and Nei 1993; Ruvulo et al. 1993). We will therefore tentatively accept this estimate of Eve's age and ask what it implies. It is often argued that if Eve lived within the past 250,000 years, then the multiregional hypothesis must be false (Stoneking 1993; Tamura and Nei 1993). Let us examine this proposition.

The age of the common ancestor of all the lineages in a population is called its coalescence time. In a randomly mating population the coalescence time for mtDNA lineages is a random variable whose mean is $2N_{eF}$ generations (Nei 1987, p. 395), where N_{eF} is the effective number of females in the population.[12] As discussed earlier, various researchers have estimated that $N_{eF} \approx 5000$. Thus the mean time to coalescence in

a randomly mating population should be 10,000 generations or perhaps 250,000 years.

The human population, however, does not mate at random. The multiregional hypothesis holds that it has long been separated into several subdivisions, which exchange genes through migration. Remarkably, subdivision and gene flow have no effect on the calculations of the preceding paragraph. The relationship of a population's effective size to its mean coalescence time remains unchanged (Nei and Takahata 1993). Population structure affects the calculations only through its effect on effective population size.

In a structured population the total effective size is related to the sum of effective subpopulation sizes, as shown in Eq. (7). For mtDNA this equation can be expressed as

$$N_F = N_{eF}(1 - F_{ST}), \tag{8}$$

where N_F is the sum of the effective numbers of females within subpopulations. For mtDNA, $F_{ST} \approx 0.3$ for the major human races (Stoneking et al. 1990; Merriwether et al. 1991), and we have already seen that $N_{eF} \approx 5000$. Thus the multiregional hypothesis implies a world population of $N_F \approx 3500$ breeding females. This agrees with the mismatch analysis, which also shows that if the initial population was structured, then it must have been even smaller (Rogers 1994b).

It is difficult to imagine that a population this small could have populated all of Europe, Africa, and Asia. If we claim that 10 times this number is required, then the mean coalescence time becomes 2.5 million years, a number that would be difficult to reconcile with the postulated convergence time of 250,000 years. Thus mitochondrial Eve is relevant to arguments about modern human origins, but in a manner somewhat different from what is usually supposed. It is not that the multiregional hypothesis requires that Eve live before 800,000 years ago, when *Homo erectus* populations spread out of Africa. Instead, knowledge that Eve lived recently would imply that the human population was small—too small to have populated three continents.

Discussion

Our review of genetic evidence has led to the following conclusions about human population history:

1. Between 33,000 and 150,000 years ago the human population expanded by more than 100-fold from an initial size of less than 7000 breeding females if the population was homogeneous or 1500 if it was structured. The small initial size accounts for the

low genetic diversity of our species, for the relatively recent age of our common mitochondrial ancestor, for the low phylogenetic resolution of mtDNA data, and for the waves evident in mtDNA mismatch distributions from most human populations.

2. Although this initial population was small, it cannot have been too small. Genetic evidence indicates that the human population never fell to 1000 individuals during the Pleistocene.
3. Many human populations separated several tens of thousands of years before the expansion that is recorded in their mismatch distributions.
4. These populations were small at some time after their separation and before the expansion documented in the mismatch distributions. These regional bottlenecks could have been brief but severe or extended but mild.

Let us now consider what these inferences imply about the origin of modern humans.

The multiregional hypothesis of modern human origins holds that humans expanded throughout the world some 800,000 years ago and have remained united by gene flow ever since. This hypothesis is inconsistent with conclusion 1. It seems impossible that 1500 females spread across three continents could have remained strongly connected by gene flow.

The replacement hypothesis holds that modern humans originated in Africa between 50,000 and 100,000 years ago and spread rapidly throughout the world replacing earlier peoples. This implies that the expansion of the modern human population occurred along with the initial separation of the races and is thus inconsistent with conclusion 3. Consequently, neither the replacement hypothesis nor the multiregional hypothesis is consistent with the genetic evidence.

The weak Garden of Eden hypothesis holds that the racial populations separated about 100,000 years ago and underwent an episode of growth about 30,000 years later. It is consistent with all the evidence reviewed here and accounts nicely for the apparent contradiction between the mismatch data (which imply that $N_e > 300{,}000$ after the expansion) and F_{ST} (which implies that $N_e < 66{,}000$). The larger number refers to the population size after the separate racial expansions, whereas the smaller number reflects the small, earlier racial populations.

But is it plausible to suppose that several widely separated populations experienced roughly simultaneous bottlenecks? This inference is surprising but not so surprising as to strain credulity. The simultaneous expansions (or bottlenecks) could have been caused by a cultural innovation that swept across the entire species, by a change in climate, or by the Toba volcanic supereruption, which apparently disrupted the cli-

mate for several years at 73,500 years B.P. (Rampino and Self 1992). In the latter two cases the disruption should have affected other species in addition to our own. This hypothesis receives support from the chimpanzee and human mismatch distributions in Figure 6, which have waves in approximately the same place.

We conclude that all available genetic evidence is consistent with the proposition that the major human populations separated from a small initial population roughly 100,000 years ago and that most of these separate populations experienced a bottleneck, or an episode of growth, several tens of thousands of years later.

Notes

[1]This estimate was obtained by Rogers and Harpending (1992) for the data of Cann et al. (1987), which we discuss further.

[2]Unless noted otherwise, "population expansion" refers to an increase in population size rather than in range.

[3]Nei (1985, p. 61) estimated the rate of mitochondrial nucleotide divergence at 1.4% per million years. If this rate is correct, then the upper bounds on all our estimates will be slightly larger.

[4]To minimize predicted between-group variance, we assume an ancient population with only two groups. The effective migration rate is then $m_e \approx 2m$, where m is the migration rate. Substituting this into Eq. (5), with $K = 2$ and $nm = 0.5$, gives $F_{ST} = 1/9$, a value several times larger than that reported from any small modern human population (Rogers and Harpending 1986).

[5]More precisely, N_{eF} is the haploid inbreeding effective number of females, defined as the reciprocal of the probability that a random pair of individuals has the same mother.

[6]Using the model of infinite sites, Li [1977, Eq. (6)] showed that

$$m(t) = \theta + [m(0) - \theta]e^{-t/N_{eF}}, \tag{9}$$

where $m(0)$ is m's initial value and t is time in generations. The half-life is obtained by setting

$$[m(t) - \theta]/[m(0) - \theta] = 1/2 \tag{10}$$

and solving for t.

[7]These results are obtained by averaging the entries on and below the diagonal of Table 2, with off-diagonal entries given twice the weight of diagonal entries.

[8]More precisely, Eq. (5) implies that there were at least 35,000 breeding females in each race, that the half-life was at least 24,000 years, and that there may have been 4 half-lives since the expansion.

[9]The eigenvalues of the migration matrix (except the first) equal $1 - 3m/2$. The effective migration rate is therefore

$$m_e = \{1 - [(1 - s)(1 - 3m/2)]^2\}/2, \tag{11}$$

where $s = 10^{-6}$ is the mutation rate per nuclear gene [Rogers and Harpending 1986, Eq. (8)]. Substituting these values into Eq. (5) and setting the result equal to 0.1 leads to

$$m = (2/3)[1 - (1 - 3/n)^{1/2}]. \tag{12}$$

Multiplying by n and expanding in Taylor series gives

$$nm \approx 1 + 3/(4n). \tag{13}$$

[10]Several researchers have found that $nm \approx 2$ (Cavalli-Sforza 1972; Nei and Roychoudhury 1982, p. 18).

[11]For example, if migration into and out of Africa were one-fifth the rate between Europe and Asia, then the half-lives would be 58% larger than those given in Table 3.

[12]The effective number of females is the reciprocal of the probability that two individuals have the same mother.

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